

Amendments to the Specification:

Add the following new paragraph before the heading "Technical Field" at page 1, line 4:

Cross Reference to Related Applications

This application is a continuation and claims the benefit of priority under 35 USC §120 of U.S. application serial number 10/301,056, filed November 21, 2002, which is a divisional of U.S. application serial number 09/383,551, filed August 26, 1999, which is a continuation-in-part of international application number PCT/JP98/00837, filed February 27, 1998, which claims the benefit of priority under 35 USC §119 of Japanese application number 10/62217, filed February 26, 1998 and Japanese application number 9/62290, filed February 27, 1997. The disclosures of the prior applications are considered part of (and are incorporated by reference in) the disclosure of this application.

Replace the paragraph beginning at page 5, line 1 with the following amended paragraph:

The ligands for CD28 and CTLA-4 are CD80 (B7-1) and CD86 (B7-2) in human and mice. CTLA-4 has about 20 times as higher affinity to both ligands as CD28. It has been elucidated that the amino acid sequence structures "MYPPPY (Met-Tyr-Pro-Pro-Tyr)" (SEQ ID NO:18) conserved through animal species is important for the binding of CD28 and CTLA-4 to CD80 (B7-1). It has also been reported that, when CD28 is stimulated, PI3 kinase (phosphoinositide 3 kinase, PI3K) associates with the phosphorylated tyrosine residue in a partial sequence "YMN~~M~~ (Tyr-Met-Asn-Met)" (SEQ ID NO:19) of CD28 "~~YMN~~M~~ (Tyr-Met-Asn-Met)~~" and that CD28 plays an important role in intracellular signal transmission through this "YxxM" structure. Furthermore, it has been reported that CTLA-4 also has a sequence represented by "YxxM," namely "YVKM (Tyr-Val-Lys-Met)" (SEQ ID NO:20) in its cytoplasmic region and that, after being stimulated, SYP associates with this sequence.

Replace the paragraph beginning at page 15, line 3 with the following amended paragraph:

- (1) A polypeptide constituting a cell surface molecule having characteristics mentioned below,
- (a) said cell surface molecule is expressed in at least thymocytes and mitogen-stimulated lymphoblast cells,
 - (b) an antibody reactive to said cell surface molecule induces adhesion between mitogen-stimulated lymphoblast cells,
 - (c) an antibody reactive to said cell surface molecule induces proliferation of peripheral blood lymphocytes under the coexistence within the presence of an antibody against CD3,
 - (d) said cell surface molecule has a partial amino acid sequence represented by Phe-Asp-Pro-Pro-Phe (SEQ ID NO:21) in its extracellular region, and
 - (e) said cell surface molecule has a partial amino acid sequence represented by Tyr-Met-Phe-Met (SEQ ID NO:22) in its cytoplasmic region.

Replace the paragraph beginning at page 31, line 17 with the following amended paragraph:

Specifically, the “cell surface molecule” of the present invention is that characterized by having, at least, properties described below;

- (a) the cell surface molecule is expressed in, at least, thymocytes and mitogen-stimulated lymphoblast cells;
- (b) an antibody reactive to the cell surface molecule induces adhesion between mitogen-stimulated lymphoblast cells;
- (c) an antibody reactive to the cell surface molecule induces proliferation of peripheral blood lymphocytes under the coexistence within the presence of an antibody against CD3;
- (d) the cell surface molecule has a partial amino acid sequence represented by Phe-Asp-Pro-Pro-Phe (SEQ ID NO:21) in its extracellular region; and

(e) the cell surface molecule has a partial amino acid sequence represented by Tyr-Met-Phe-Met (SEQ ID NO:22) in its cytoplasmic region.

Replace the paragraph beginning at page 34, line 3 with the following amended paragraph:

To determine percent homology between two sequences, the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci. USA* 87:2264-2268, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5877 is used. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul, et al. (1990) *J. Mol. Biol.* 215:403-410. BLAST nucleotide searches are performed with the NBLAST program, score = 100, word length = 12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches are performed with the XBLAST program, score = 50, word length = 3 to obtain amino acid sequences homologous to a VRK1 or VRK2 protein molecules. To obtain gapped alignments for comparison purposes, Gapped BLAST is utilized as described in Altschul et al. (1997) *Nucleic Acids Res.* 25:3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) are used. See web site of National Center for Biotechnology Information (NCBI), which is a division of National Library of Medicine (NLM) at the National Institutes of Health of USA <http://www.ncbi.nlm.nih.gov>.

Replace the paragraph beginning at page 74, line 21 with the following amended paragraph:

Figure 10 shows the homology among amino acid sequences of human (SEQ ID NO:2), rat (SEQ ID NO:13), and mouse "JTT-1 antigen" (SEQ ID NO:14) and "rat JTT-1 antigen" mutant (SEQ ID NO:15) (the consensus sequence is listed as SEQ ID NO:16).

Replace the paragraph beginning at page 74, line 24 with the following amended paragraph:

Figure 11 shows the homology among amino acid sequences and conservation state of motifs in “human JTT-1 antigen,” “human CD28 molecule”, and “human CTLA-4 molecule:” (SEQ ID NOs:2, 25, and 26, respectively) (the consensus sequence is listed as SEQ ID NO:17).

Replace the paragraph beginning at page 74, line 28 with the following amended paragraph:

Figure 12 schematically shows the protein secondary structure of, and their similarity among “human JTT-1 antigen,” (SEQ ID NOs:21 and 22), “human CD28 molecule,” (SEQ ID NOs:18 and 19), and “human CTLA-4 molecule:” (SEQ ID NOs:18 and 20).

Replace the paragraph beginning at page 75, line 1 with the following amended paragraph:

Figure 14 shows the difference in amino acid sequences between “rat JTT-1 antigen” and its alternative splicing mutant (SEQ ID NOs:13 and 15, respectively) (the consensus sequence is listed as SEQ ID NO:23).

Replace the paragraph beginning at page 84, line 4 with the following amended paragraph:

After the purified “JTT-1 antigen” was subjected to SDS-PAGE, the N-terminal amino acid sequence was determined by the usual method. The result revealed that “JTT-1 antigen” contained an amino acid sequence Glu-Leu-Asn-Asp-Leu-Ala-Asn-His-Arg (amino acid residues 21-29 of SEQ ID NO:13).

Replace the paragraph beginning at page 88, line 15 with the following amended paragraph:

The nucleotide sequence of clone "T132A7" was determined by dideoxy method with "Auto Read Sequencing Kit" (Pharmacia) and "A.L.F. DNA Sequencer" (Pharmacia). In addition, the deduced amino acid sequence of "rat JTT-1 antigen" encoded by the nucleotide sequence was analyzed with gene analysis software "GENEWORKS" (IntelliGenetics). The nucleotide sequence and the deduced amino acid sequence were shown in SEQ ID NO: 4 and SEQ ID NO:13, respectively.

Replace the paragraph beginning at page 94, line 10 with the following amended paragraph:

The nucleotide sequences of each of the five clones were determined by dideoxy method with "Auto Read Sequencing Kit" (Pharmacia) and "A.L.F. DNA Sequencer" (Pharmacia). The four of the five clones comprise the same nucleotide sequence. The nucleotide sequence of cDNA encoding the full length of "mouse JTT-1 antigen" and the deduced amino acid sequence are shown in SEQ ID NO: 5 and SEQ ID NO:14, respectively.

Replace the paragraph beginning at page 97, line 22 with the following amended paragraph:

The nucleotide sequences of the two clones were determined by dideoxy method with "Auto Read Sequencing Kit" (Pharmacia) and A.L.F. DNA Sequencer (Pharmacia). The two clones comprise the same nucleotide sequence. The nucleotide sequence of cDNA encoding the full length of the obtained "rat JTT-1 antigen" and the deduced amino acid sequence are shown in SEQ ID NO: 6 and SEQ ID NO:15, respectively. The amino acid sequence (SEQ ID NO: 6 or SEQ ID NO:15) deduced from the obtained cDNA sequence was compared with the amino acid sequence (SEQ ID NO: 4 or SEQ ID NO:13) deduced from the obtained cDNA sequence encoding "rat JTT-1 antigen" cloned in Example 7 (Figure 14). As shown in Figure 14, the amino acid sequence encoded by the cDNA cloned in this test was completely the same as that

encoded by the cDNA encoding “rat JTT-1 antigen” obtained in Example 7, except that (1) C-terminal three continuous amino acid residues (Met-Thr-Ser) changes into Thr-Ala-Pro, and that (2) subsequent to the Thr-Ala-Pro, 16 continuous amino acid residues (Leu-Arg-Ala-Leu-Gly-Arg-Gly-Glu-His-Ser-Ser-Cys-Gln-Asp-Arg-Asn) (SEQ ID NO:24) are added. This indicates that the cDNA cloned in this test encodes the alternative splicing variant of “rat JTT-1 antigen” obtained in Example 7.

Replace the paragraph beginning at page 105, line 21 with the following amended paragraph:

In order to amplify the cDNA encoding the extracellular region of “rat JTT-1 antigen” by PCR, 5' primer having XhoI restriction site (5'-CTGCTCGAGATGAAGCCCTACTTCTCG-3', SEQ ID NO: 7) and 3' primer having BamHI restriction site (5'-ACCCTACGGGTAACGGATCCTTCAGCTGGCAA-3', SEQ ID NO:8) at their terminus were designed and synthesized. Using cDNA clone “T132A7” obtained in Example 7 encoding the full length of “rat JTT-1 antigen” as a template, PCR was performed with the primers to prepare the cDNA comprising the cDNA encoding the extracellular region of “rat JTT-1 antigen” having XhoI and BamHI restriction sites at its both ends. The PCR products so obtained were digested with XhoI and BamHI and separated by agarose gel electrophoresis to isolate an about 450-bp band predicted to be the cDNA fragment encoding a desired extracellular region. The isolated cDNA fragment was subcloned into pBluescript II SK (+) (Stratagene) cleaved with XhoI and BamHI. Sequence analysis with an automated fluorescence DNA sequencer (Applied Biosystems) revealed that the cDNA fragment comprises the region encoding amino acid sequence corresponding to the amino acid residues 1 to 141 of “rat JTT-1 antigen” (SEQ ID NO: 4 or SEQ ID NO:13).